**Project Information**

**Project Title**

Comprehensive molecular profiling in cholangiocarcinomas for better treatment selection: A Prospective Study

**Amount Requested**

50,000

**Applicant Information**

**Applicant Name**

Grainne Mary O'Kane

**Degree (Select all that apply)**

- MD

**Academic Level (Select all that apply)**

- Post-Doc Fellow

**Institution Information**

**Institution Name**

Princess Margaret Cancer Centre

**Institution City**

Toronto

**Institution State**

ON - Ontario

**Institution Country**

Canada

**Email**

Grainne.O'Kane@uhn.ca

**Mentor Information**

**Mentor Name**

Jennifer Knox

**Mentor Title**
Cholangiocarcinomas (CCs) comprise a heterogeneous group of malignancies, which can be divided into intra-hepatic CCs (IHCC) and extrahepatic CCs (EHCCs). Risk factors include liver fluke infection, chronic inflammatory disorders and hereditary syndromes. Progress in the treatment of CC has been limited and the pathogenesis is poorly understood. Chemotherapy remains the mainstay of treatment. Despite classification according to anatomical site, increasing evidence suggests specific molecular subtypes. A number of putative targets have already been discovered through next generation sequencing, CCs are therefore an attractive group for trials.

Methods: Patients will be included if they have advanced/inoperable CC at diagnosis or have progressed post adjuvant treatment. A fresh biopsy will be obtained prior to chemotherapy for whole genome and transcriptome analysis. Mutations and potential signatures will be identified (6 weeks post biopsy) and correlated with response to chemotherapy. In patients who have progressed post first line chemotherapy, profiling will help align patients to appropriate 2nd line trials ongoing at the Princess Margaret Cancer Centre (PM) to allow for a personalized approach. Expected outcomes: Much research has focused on sequencing. This prospective study will assess disease response and therefore has the potential to identify which molecular subgroups benefit from standard chemotherapy and moreover which do not.

This is a prospective study where fresh tumor materials, a whole blood sample for germ line DNA analysis and serial plasma and serum samples will be acquired from patients with advanced CC undergoing 1st line therapy with gemcitabine or 5-fluorouracil (5-FU) regimens. The study will aim to initially enrol 30 patients with planned accrual of 200 patients incorporating advanced gallbladder cancers (GBCs) at a later stage. Although GBCs have a distinctly different pathogenesis, given the relative rarity of these cancers these will be included in the final study. Patients must have at least one tumor lesion amenable to biopsy prior to treatment begins. Whole genome and transcriptome analysis will take place onsite at the PM. Results will be available 6-8 weeks post biopsy in alignment with other clinical trials ongoing at this centre. Serum CA19.9 and hepatitis serology will also be measured at baseline. CA19.9 will continue to be measured approximately every 8-9 weeks thereafter as part of standard of care until disease progression is confirmed. Radiological assessment of tumors will be performed at baseline using a CT or MRI scan and disease response to therapy will be assessed every 8-9 weeks using the same imaging modality and RECIST 1.1. At the time of radiological disease progression, a further tumor biopsy will be collected to study potential changes in the molecular characteristics of tumors under the selection pressure of first line therapy, if safe and feasible.

Cholangiocarcinoma (CC) is a cancer of the bile ducts, which often presents in at a late stage and is highly fatal. Currently we treat inoperable and advanced CC with chemotherapywith survival on average less than 1 year. CCs however are a heterogeneous group and patients respond differently to chemotherapy with no predictors of response or resistance. Analysis of the DNA in CCs to date has shown that different events can occur at the gene level that may be responsible for developing CC. Some CCs may have multiple mutations, which can lead to an unstable tumor. Identification of events that initiate and drive cancer is important as these may be targets for drug therapy or immune therapy. Some tumors may not be responsive to chemotherapy and it's also important to know this so that patients do not undergo treatment associated with toxicity that may disimprove quality of life or survival. This study looks comprehensively at the genetic makeup of the participating patients tumor prior to commencing chemotherapy. Results of profiling will be available 6-8 weeks post biopsy. By doing this we can identify which types of cholangiocarcinoma should be treated with chemotherapy and which should not. Further more we can identify potential drug targets. This may enable us to refer patients to our phase 1 drug development program for potential enrolment on trials after their cancer has progressed on standard treatment.
Specific Aims (2500 Max Characters)

The primary objective in this study is to assess the feasibility of prospectively identifying subgroups of patients with advanced CC who have distinct genomic characteristics for better treatment selection while undergoing 1st-line palliative chemotherapy. We will assess patient outcomes to chemotherapy as determined by disease control rate (complete response, partial response and stable disease >= to 24 weeks) according to specific molecular profiles.

Other specific aims include:
1. To determine potential germline mutations that may account for the development of CC.
2. To identify potential predictive biomarkers of response to immunotherapy in CC including mismatch repair (MMR)-deficiency and high mutational or neo-antigen burden
3. To identify other rare but potentially targetable mutations including ARID1A, CDKN2A, CDKN2b, Her2, EGFR, FGFR fusions, RNF43 and BRAF.
4. To track the clinical outcomes including toxicities in locally advanced or metastatic CC cancer clinical trials or treatments patient is receiving.

Background and Significance (3000 Max Characters)

Cholangiocarcinomas (CC) comprise a heterogeneous group of malignancies that present at an advanced stage disease where chemotherapy is the mainstay of treatment and survival is less than one year. The only phase III trial, the ABC 02 trial, revealed superiority of gemcitabine/cisplatin over gemcitabine alone in patients with metastatic disease, which remains the current standard of care.3 Other combinations have demonstrated activity 6-10 but have not been evaluated in the phase III setting. There are no large prospective trials in second line to guide treatment selection. Prognostic factors include stage, haemoglobin, neutrophil to lymphocyte ratio and bilirubin.12,13 Expression of hENT1 and polymorphisms in cytidine deaminase may predict response to gemcitabine regimens 14,15 however a biomarker in clinical practice has not been established. Molecular profile and gene expression analyses have however improved our understanding of the genomic landscape. This has paved the path to a more personalized approach. IDH1/2 substitutions and FGFR fusions may be more prevalent in IHCC and a number of trials investigating targeted agents are enrolling.2,19,24 Ponatinib has demonstrated efficacy in an IHCC patient harbouring a FGFR2-MGEA5 fusion.25 A phase II study is accruing (NCT02265341). Other potential targets include CDK 4/6 inhibitors 17 ARID1A and genes involved in chromatin remodelling.18 Our group are currently investigating targeting the RAS/Mek pathway in a phase II study of selumetinib scheduling in combination with GEMCIS as first line treatment for advanced which has previously shown promise. 21 BRAF mutations may be restricted to IHCC 22; a case report has demonstrated dramatic responses with combined dabrafenib and trametinib. 23 The role of immune checkpoint inhibitors (ICIs) in CC is largely unknown. Impressive responses have been demonstrated in small numbers of biliary tract cancers with mismatch repair-deficiency (MMRd) which have high mutational loads.34 In virally driven malignancies ICIs are producing dramatic responses36, suggesting that chronic inflammation and inflammatory signatures may be predictive of response to immune checkpoint blockade. Despite the emerging information on individual genetic drivers there is a paucity of information on mutational signatures in CC largely owing to small numbers in studies. An APOBEC-mediated mutational signature, correlating with APOBEC3 expression and higher mutational loads, has recently been proposed as a major driver of EHCC by the Japanese group.2 Sia et al has proposed a proliferative and an inflammatory signature within IHCCs only.37 None of these mutations and signatures have prospectively been assessed as markers of response to chemotherapy. This study seeks to establish biomarker directed therapies for patients with advanced CC in real-time at PM. This study can teach us how to utilise the information determined by comprehensive profiling in the clinical setting.

Project Timeline (2500 Max Characters)
2017 Research Fellowship Application : Entry #
11027

Milestone/Activity: Submission of protocol for coordinated institutional approval:
Expected Date: 1-Dec-2016

Milestone/Activity: Health Canada Approval
Expected Date: 1-Jan-2017

Milestone/Activity: 1st patient accrued
Expected Date: 1-03-17

Milestone/Activity: Interim analysis of genomic and transcriptome data (N=15)
Expected date: 1-8-17

Milestone/Activity: Accrual complete, 1st stage N= 30
Expected Date: 1-01-2018

Literature Cited

Budget

Impact or Collab Award
I want to apply for an Impact Award (up to $50,000)

Impact Applicant Name
Grainne O'Kane

Impact App Title
Dr.

Impact App Institution
### 2017 Research Fellowship Application : Entry #11027

**Princess Margaret Cancer Centre**

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<th>Impact App Personnel 1 Name</th>
<th>Clinical trials nurse specialist TBC</th>
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**Impact Per 1 Base Salary**

84542.00

**Impact Per 1 Salary Requested**

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**Impact Per 2 Base Salary**

65661.00

**Impact Per 2 Salary Requested**

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**Impact App Personnel Total**

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**Impact Travel List**

**Description**

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**Amount ($)**

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# 2017 Research Fellowship Application : Entry #11027

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## Impact Other Expenses

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**Impact Total Requested**

49050